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SPECIAL ARTICLE

ESMO Consensus Conference on malignant lymphoma: management of 'ultra-high-risk' patients

M. Hutchings[1*], M. Ladetto[2], C. Buske[3], P. de Nully Brown[1], A. J. M. Ferreri[4], M. Pfreundschuh[5†], N. Schmitz[6], A. Sureda Balari[7], G. van Imhoff[8], J. Walewski[9] & the ESMO Lymphoma Consensus Conference Panel Members[‡]

[1]Department of Hematology, Rigshospitalet, Copenhagen, Denmark; [2]Hematology Division, Azienda Ospedaliera Santi Antonio e Biagio e Cesare Arrigo, Alessandria, Italy; [3]Comprehensive Cancer Center Ulm and Department of Internal Medicine III, Institute of Experimental Cancer Research University Hospital, Ulm, Germany; [4]Department of Onco-Hematology Medicine, Unit of Lymphoid Malignancies, IRCCS San Raffaele Scientific Institute, Milan, Italy; [5]Innere Medizin I, University Klinik des Saarlandes, Hamburg; [6]Department of Hematology, Oncology and Stem Cell Transplantation, Asklepios Klinik St. Georg, Hamburg, Germany; [7]Servei d'Hematologia, Institut Català d'Oncologia – Hospital Duran i Reynals, Barcelona, Spain; [8]Department of Hematology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands; [9]Department of Lymphoid Malignancies, Maria Sklodowska-Curie Institute – Oncology Center, Warsaw, Poland

Correspondence to: Dr Martin Hutchings, ESMO Guidelines Committee, ESMO Head Office, Via Ginevra 4, 6900 Lugano, Switzerland.
E-mail: clinicalguidelines@esmo.org

[†]Deceased.

[‡]See appendix for members of the ESMO Lymphoma Consensus Conference.

The European Society for Medical Oncology (ESMO) consensus conference on malignant lymphoma was held on 20 June 2015 in Lugano, Switzerland, and included a multidisciplinary panel of 25 leading experts. The aim of the conference was to develop recommendations on critical subjects difficult to consider in detail in the ESMO Clinical Practice Guidelines. The following areas were identified: (1) the elderly patient, (2) prognostic factors suitable for clinical use and (3) the 'ultra-high-risk' group. Before the conference, the expert panel was divided into three working groups; each group focused on one of these areas in order to address clinically relevant questions relating to that topic. All relevant scientific literature, as identified by the experts, was reviewed in advance. During the consensus conference, each working group developed recommendations to address each of the questions devised by their group. These recommendations were then presented to the entire multidisciplinary panel and a consensus was reached. This manuscript presents recommendations regarding the management of the following 'ultra-high-risk' situations: (1) early central nervous system relapse of diffuse large B-cell lymphoma, (2) primary refractory Hodgkin lymphoma and (3) plasmablastic lymphoma. Results, including a summary of evidence supporting each recommendation, are detailed in this manuscript. All expert panel members approved this final article.

Key words: lymphoma, consensus, high-risk, aggressive, primary resistance, relapse

Introduction

Despite the high chemosensitivity of aggressive B-cell lymphomas, a large proportion of patients still respond poorly to therapy and eventually die from their disease. A number of clinical and pathological factors define groups of patients who are at very high risk of such treatment failure. For these 'ultra-high-risk' patients, there is no international consensus regarding the optimal management approach.

In 2015, the European Society for Medical Oncology (ESMO) held a consensus conference on malignant lymphoma in order to develop recommendations on critical subjects that were difficult to consider in detail in the ESMO Clinical Practice Guidelines (CPGs). In this consensus conference, one of the working groups focussed on ultra-high-risk patients. As such, the objectives of this working group were: (1) to identify a number of ultra-high-risk patient categories where guidelines were lacking and a consensus on management was likely to be reached; (2) to critically review the available literature describing the management of these patient groups; (3) to provide recommendations on the management of ultra-high-risk patients in the context of clinical

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Table 1. Levels of evidence and grades of recommendation[a]

Levels of evidence

I	Evidence from at least one large randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomised trials without heterogeneity
II	Small randomised trials or large randomised trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case–control studies
V	Studies without control group, case reports, experts' opinions

Grades of recommendation

A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, . . .), optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

[a]By permission of the Infectious Diseases Society of America-United States Public Health Service Grading System [2].

research and routine practice. Here we describe the recommendations developed and provide a summary of evidence supporting each recommendation.

Methods

A consensus panel, comprising a multidisciplinary group of 25 experts in the management of lymphoma, was convened by ESMO. Three consensus conference chairs (**C. Buske, M. Ladetto and M. Hutchings**) were also appointed. The consensus panel was divided into three working groups, each of which was assigned a specific subject area and a working group chair as follows:

1. The elderly patient (Chair: **C. Buske**)
2. Prognostic factors suitable for clinical use (Chair: **M. Ladetto**)
3. The 'ultra-high-risk' group (Chair: **M. Hutchings**)

The consensus conference was held on 20 June 2015 in Lugano, Switzerland. Before this consensus conference, three to four clinically-relevant questions were identified for each subject area. For working group 3, the following three areas relating to the management of 'ultra-high-risk' patients with malignant lymphoma were identified for discussion:

1. How to predict, prevent and treat early central nervous system (CNS) relapse after first-line treatment of diffuse large B-cell lymphoma (DLBCL)
2. Management of primary resistant Hodgkin lymphoma (HL)
3. Management of plasmablastic lymphoma (PBL)

The selection of these three areas was a result of thorough discussions in the working group, where we agreed that these were areas of particular clinical importance with a lack of clear consensus. It is acknowledged that this selection does not cover all important high-risk situations in lymphoma management. We considered including the management of double-hit DLBCL, but eventually this topic was omitted since (1) this would require a full paper of its own, and (2) it is already covered by a number of separate guidelines, including the ESMO CPG for DLBCL [1].

A literature review was conducted by each working group before the consensus conference, with each group responsible for compiling a summary of relevant information required to develop recommendations relating to each of their questions at the conference. No systematic literature search was undertaken. During the conference, in parallel sessions, the three working groups discussed and agreed on recommendations relating to each of their assigned questions. The level of evidence and strength of each recommendation was also noted, which were defined based on an adapted version of the 'Infectious Diseases Society of America-United States Public Health Service Grading System', as presented in Table 1 [2]. Recommendations from each group were then presented to the entire panel of experts, where they were discussed and modified as required. Finally, a vote was conducted to determine the level of agreement amongst the expert panel for each of the recommendations. Panel members were allowed to abstain from voting.

Results from the section of the consensus conference dedicated to the management of 'ultra-high-risk' patients with malignant lymphoma, together with a summary of evidence supporting each recommendation, are detailed in this article, and a summary of these recommendations is included in Table 2. However, these additional recommendations should be read in conjunction with the already-published ESMO CPGs for the diagnosis, treatment and follow-up of malignant lymphomas [1, 3–8].

Results

1. How to predict, prevent and treat CNS relapse of systemic DLBCL

Risk of CNS disease. Estimation of the individual patient's risk of CNS disease [defined as progression during or recurrence after first-line treatment with involvement of the brain parenchyma or cerebrospinal fluid (CSF)] is largely based on reports from single institutions [9, 10] and cooperative groups [11]. During the last

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Table 2. Summary of recommendations

Guidelines statement	LoE	GoR	Consensus
1. How to predict, prevent and treat early CNS relapse after first-line treatment of DLBCL			
Recommendations:			
1.1 IPI parameters (age >60 years, high LDH levels, poor PS, advanced disease stage and more than one extra-nodal site) are risk factors for early CNS relapse following first-line treatment of DLBCL, with a direct relationship between the number of unfavourable features and the CNS risk. The involvement of the testes, kidneys, adrenals, breast, bone marrow and bone has also been reported to increase the risk of CNS disease.	II	B	100% yes (18 voters)
1.2 Patients with DLBCL considered as high risk for CNS relapse should be assessed by brain MRI and CSF assessment by conventional cytology examination and flow cytometry	III	C	100% yes (18 voters)
1.3 There is little or no role for i.t. chemotherapy for patients with DLBCL considered as high risk for CNS relapse. i.v. prophylaxis is an option for high-risk patients without evidence of CNS involvement, even though the level of supporting evidence is low. Patients with MRI or CSF evidence of CNS involvement at presentation should receive a combination of anti-lymphoma drugs with good CNS bioavailability, aimed at controlling both CNS and systemic disease, preferably within a clinical trial	III	C	100% yes (18 voters)
2. Management of primary resistant HL			
Recommendations:			
2.1 For patients with primary resistant HL, there is no evidence to suggest a benefit from treating any differently to other patients with relapsed Hodgkin lymphoma. As such, these patients should be treated the same as other patients with relapsing HL, preferably as part of a clinical trial	III	D	100% yes (18 voters)
2.2 The use of BV and CPIs seem to be particularly beneficial for patients with primary resistant HL who are less likely to benefit from conventional therapies. Consolidation with BV after HDT and ASCT is recommended for patients with primary resistant HL	II	B	No vote obtained
2.3 AlloSCT has a limited role for patients with primary resistant HL but can be considered in selected patients with a good, durable remission and a suitable donor	IV	D	100% yes (18 voters)
3. Management of PBL			
Recommendations:			
3.1 For HIV-negative patients with suspected PBL, diagnostic assessment should include an IHC panel of CD38, CD20, PAX5, CD138, EBER, CD30, MUM-1, Kappa-lambda, HHV8 and ALK	IV	C	100% yes (18 voters)
3.2 HIV-negative patients with PBL should be treated the same as other high-risk subtypes of DLBCL, although rituximab should not be used	IV	C	100% yes (18 voters)
3.3 Although bortezomib can be safely combined with CHOP, this has not led to improved outcomes and further studies are required	V	C	100% yes (18 voters)
3.4 HD-ASCT may play a role in the management of PBL but further studies are required, since available data are from casuistic reports of selected patients	IV	D	100% yes (18 voters)

alloSCT, allogenic stem cell transplant; ASCT, autologous stem cell transplantation; BV, brentuximab vedotin; CHOP, cyclophosphamide/doxorubicin/vincristine/prednisone; CNS, central nervous system; CPI, checkpoint inhibitor; CSF, cerebrospinal fluid; DLBCL, diffuse large B-cell lymphoma; EBER, Epstein–Barr virus-encoded RNA; GoR, grade of recommendation; HD-ASCT, high-dose autologous stem cell transplantation; HDT, high-dose therapy; HIV, human immunodeficiency virus; HL, Hodgkin lymphoma; IHC, immunohistochemistry; IPI, International Prognostic Index; i.t., intrathecal; i.v., intravenous; LDH, lactate dehydrogenase; LoE, level of evidence; MRI, magnetic resonance imaging; PBL, plasmablastic lymphoma; PS, performance status.

decade, a number of investigators either conducted post-hoc analyses of CNS relapses occurring in patients with DLBCL who had been treated in prospective randomised studies [12–14], or analyses carried out on other cohorts of patients with aggressive B-cell lymphoma – most commonly DLBCL [15–21]. These studies varied in several ways, including the varying definitions used for high-risk CNS disease, differing imaging technologies, differing means of assessing CSF involvement, and differing recommendations for CNS relapse prophylaxis. These differences influenced not only the percentages of patients diagnosed with CNS relapse, but also the identification of CNS risk factors and the analyses of the value of intrathecal (i.t.) prophylaxis.

Table 3 summarises findings of larger studies (>200 patients) in patients with aggressive B-cell lymphoma. Risk factors listed are those identified via multivariate analyses of patients treated with R-CHOP (rituximab/cyclophosphamide/doxorubicin/vincristine/prednisone). Collectively, these data demonstrate that secondary CNS involvement is a relatively rare complication of DLBCL, occurring in 2.3%–8.4% of patients. The relatively large variation in frequencies of CNS disease reported by different authors most likely reflect different patient characteristics, particularly differences in age and distribution of International Prognostic Index (IPI) factors. The randomised RICOVER-60 trial demonstrated that the addition of rituximab significantly reduced the incidence of CNS disease [12]; nevertheless, the effect of rituximab appears to be moderate, and the problem presented by CNS disease remains unresolved. The risk factor analyses presented in Table 3, as well as those from other smaller studies from

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Table 3. Risk factors for CNS disease in patients with DLBCL[a] using (R)-CHOP and variants

Study	Patients[b]	IPI	↑LDH[c]	>1 ENS[c]	Advanced stage[c]	Extranodal site[c]		Other[c]
Tomita et al. [21]	82/1221 (6.7%)	NS	NS	NS	NS	Breast Adrenal Bone	10.5 4.6 2.0	Age >60 : 2.1
Schmitz et al. [14]	14/620 (2.3%)	NA	3.8	NS	5.4	NS		R: 0.3, not in high-risk patients
Boehme et al. [12]	22/608 (3.6%)	NR	S	S	NS	NR		ECOG PS >1
Tai et al. [18]	19/320 (6.0%)	NS	NS	NS	NS	Kidney Testis Breast	20.1 6.7 6.1	ECOG PS >1 : 2.0 non-CR 3.3
Villa et al. [19]	19/309 (6.1%)	NS	NS	NS	Stage IV 8.0	Kidney	3.3	
Shimazu et al. [17]	20/238 (8.4%)	NR	2.4	2.0	NS	Marrow	2.1	Age >60 : 2.5
Guirguis et al. [16]	8/214 (3.7%)	NS	NS	NS	NS	Testis	33.5	None
Yamamoto et al. [20]	81/203 (3.9%)	NS	NS	NS	NS	NS		
Chihara et al. [15]	9/203 (4.4%)	NS	NS	Any ENS 2.9	NS	NS		Bulk > 7.5 cm: 3.34 ALC $<1.0 \times 10^9$/L: 2.38
Feugier et al. [13]	11/202 (5.4%)	S	S	NS	NS	NS		ECOG > 1
Ferreri et al. [107]	10/200 (5%)	S	S	NS	S	Testis, breast, kidney, adrenal glands, paranasal sinus		
Schmitz et al. [22]	71/1597 (4.4%)	S	S	NS ($P = 0.057$)	S	Kidney, adrenal glands, bone marrow, testes, pericardium, orbit		

[a]Studies by Schmitz et al. and by Boehme et al. contain approximately 15% of patients with other aggressive B-cell lymphomas (blastoid mantle cell lymphoma, follicular lymphoma grade 3).
[b]Patients with CNS disease/patients on study.
[c]Numbers are hazard ratios reported from multivariate analyses.
ALC, absolute lymphocyte count; CHOP, cyclophosphamide/doxorubicin/vincristine/prednisone; CNS, central nervous system; CR, complete response; DLBCL, diffuse large B-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; ENS, extranodal site; IPI, International Prognostic Index; LDH, lactate dehydrogenase; N/A, not applicable; NR, not reported; NS, not significant; R, rituximab; S, significant.

the rituximab and pre-rituximab eras, show that individual IPI factors [age >60 years, high lactate dehydrogenase (LDH) levels, poor performance status (PS), advanced disease stage and more than one extranodal site], and various combinations thereof, have a significant impact on the risk of CNS disease. In addition, involvements of the testes, kidneys, adrenals, breast, bone marrow and bone have been reported to increase the risk of CNS disease.

A large study of 2196 patients treated with R-CHOP or R-CHOEP (rituximab/cyclophosphamide/doxorubicin/vincristine/etoposide/prednisone) in prospective trials conducted by the German High-Grade non-Hodgkin Lymphoma Study Group (Deutsche Studiengruppe für Hochmaligne Non-Hodgkin-Lymphome; DSHNHL) [14] showed that the presence of any of the five IPI factors and involvement of the kidneys/adrenals increased the risk of CNS disease. Still, even the ~6% of patients with four to six risk factors had a 2-year rate of CNS disease of no more than 10%. This model was validated using an independent data set from British Columbia [22] and, more recently, in an international cohort of 1290 positron emission tomography (PET)-computed tomography (CT)-staged patients [23].

Biological risk factors such as *MYC* translocation, double-hit lymphomas or the presence of certain adhesion molecules on lymphoma cells have more recently been associated with an increased risk for CNS disease [24–27].

Prophylaxis of CNS disease. Traditionally, prophylaxis of CNS disease in DLBCL consists of i.t. injections of methotrexate (MTX), cytarabine (Ara-C), prednisone/prednisolone, or combinations thereof. However, i.t. chemotherapy does not reach measurable concentrations in the brain parenchyma, and thus the general concept of i.t. prophylaxis in patients with DLBCL is controversial. For patients treated with R-CHOP, there is increasing evidence from several recent studies (summarised in Table 4) that i.t. prophylaxis is not effective [28, 29]. Given the serious

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Table 4. Prophylaxis of CNS relapses in studies using (R)-CHOP and variants for treatment of DLBCL

Study	Number of patients	Systemic/i.t. treatment	CNS prophylaxis	CNS relapses (%)
Schmitz et al. [14]	2196 (1576 w/o R, 620 w/ R)	(R)-CHO(E)P[a] i.t. MTX	BM, testis, head, sinuses, orbits, oral cavity, tongue and salivary glands	2.6% (all pts)
Boehme et al. [12]	1222 (612 w/o R, 610 w/ R)	(R)-CHOP i.t. MTX	BM, testis, head, sinuses, orbits, oral cavity, tongue and salivary glands	2.5% (w/o prophylaxis) 4.4% (w/ prophylaxis)
Kumar et al. [108]	989 (all w/ R)	R-CHOP i.t. MTX ± Ara-C, i.v. MTX	At the discretion of investigator	2.1% (w/o prophylaxis) 10.9% (w/ prophylaxis)
Tai et al. [18]	499 (179 w/o R, 320 w/ R)	(R)-CHOP i.t. MTX	>1 ENS, orbits, sinuses, breast, testis, bone, BM	5% (w/o prophylaxis) 11% (w/ prophylaxis)
Tomita et al. [29]	322 (all w/ R)	R-CHOP i.t. MTX	↑ LDH, bulk >10, PS ≥ 2, BM, nasal, bone, breast, skin, testis	2.8% (w/o prophylaxis) 7.5% (w/ prophylaxis)
Arkenau et al. [28]	259 (177 w/o R, 62 w/ R)	(R)-CHOP (R)-PmitCEBO i.t. MTX ± Ara-C	BM, testis, sinuses, orbits, bone, blood	1.1% (CI 0%–2.5%) 2 pts w/o prophylaxis 1 pt w/ prophylaxis
Guirguis et al. [16]	214 (all w/ R)	R-CHOP i.t. MTX (25 pts), i.v. MTX (17 pts)	↑ LDH, >1 ENS, testis, epidural, sinuses or skull	2% (w/o prophylaxis) 1.9% (w/ prophylaxis)
Ferreri et al. [107]	200 (all w/ R)	R-CHOP i.v. MTX (33 pts)	Testis, breast, sinuses, orbits, nasopharynx Advanced stage + ↑ LDH	12% (w/o prophylaxis) 0% (w/ i.v. MTX)

[a]Includes patients treated with higher doses of cyclophosphamide, doxorubicin and etoposide and patients treated with dose-escalated sequential HDT and rituximab.

Ara-C, cytarabine; BM, bone marrow; CHOP, cyclophosphamide/doxorubicin/vincristine/prednisone; CI, confidence interval; CNS, central nervous system; DLBCL, diffuse large B-cell lymphoma; E, etoposide; ENS, extranodal site; HDT, high-dose therapy; i.t., intrathecal; i.v., intravenous; LDH, lactate dehydrogenase; MTX, methotrexate; NR, not reported; PS, performance status; pt, patient; R, rituximab; R-PMitCEBO, rituximab/prednisolone/mitoxantrone/cyclophosphamide/etoposide/bleomycin/vincristine; w/, with; w/o, without.

toxicities (leukopenia, infections, mucositis) related to i.t. injections of cytotoxic drugs [30, 31], this practice should be restricted to very high-risk patients or abandoned altogether. The only exception may be for patients with involvement of the testes where i.t. prophylaxis should be administered in conjunction with specific systemic treatment and local radiotherapy (RT) [32]. For all other organs involved (bone marrow, bone, paranasal sinuses, breast, skin, etc.), the evidence supporting the use of i.t. prophylaxis is very scarce.

The comparative efficacy of alternative strategies, such as systemic high-dose MTX (HD-MTX; >1.5 g/m^2), in preventing CNS progression or relapse is currently undergoing clinical evaluation. The results of the French studies with (R)-ACVBP (rituximab/doxorubicin/cyclophosphamide/vindesine/bleomycin/prednisone) [33, 34] and phase II studies using one or two courses of HD-MTX in patients treated with R-CHOP [35, 36] indicate that this treatment is effective and should be the prophylactic therapy of choice in high-risk patients fit enough to tolerate the associated toxicities. For elderly patients, not only is the dose important but the duration of intravenous (i.v.) infusion as well. For these patients, the duration of HD-MTX infusion should not exceed 4 hours, in which case it is usually well tolerated [37, 38]. In the ACVBP (doxorubicin/cyclophosphamide/vindesine/bleomycin/prednisone) versus CHOP trial conducted by Tilly et al. [33], in patients between the ages of 61 and 69 years, there were significantly fewer isolated CNS relapses in the ACVBP arm, with two i.v. high-dose MTX (3 g/m^2) infusions, than in the CHOP arm. However, this dose of MTX may be poorly tolerated in patients over the age of 70 years. According to the German High-Grade Lymphoma Study Group, a HD-MTX dose of 1.5 g/m^2, dose-adjusted according to creatinine clearance and given intravenously before the first and after the last R-CHOP, is well tolerated in patients above 70 years of age [39].

Treatment of CNS disease. I.t. injections, whole brain RT and systemic administration of cytotoxic drugs not crossing the blood–brain barrier (BBB), have largely been ineffective in the treatment of secondary CNS lymphoma (SCNSL) [40, 41]. The inclusion of drugs which cross the BBB, such as HD-MTX and Ara-C, has produced encouraging results from studies of patients with primary CNS lymphomas [42, 43], resulting in measurable benefits and significantly longer survival. To date, virtually all other drugs known to cross the BBB (procarbazine, etoposide, ifosfamide, thiotepa, carmustine and others) have been used mostly in combination with MTX and/or Ara-C to further improve results [38, 44, 45]. As seen with MTX and Ara-C, most other drugs

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seem to also be most effective at high doses, and thus require autologous haematopoietic stem cell transplantation (HSCT). Consequently, the most recent and successful protocols to treat primary and SCNSL consist of complex treatment algorithms encompassing two or more courses of HD-MTX and/or Ara-C administered together with other BBB-crossing agents, followed by high-dose therapy (HDT) combining BBB-crossing agents such as carmustine, thiotepa, busulfan or etoposide, which can be dose-escalated if HSCT is conducted [38, 44, 46, 47]. The first prospective phase II study demonstrating the potential of this strategy was reported by Korfel et al. [44]. Patients up to 65 years of age received induction chemotherapy with HD-MTX, ifosfamide and dexamethasone followed by HD-Ara-C, thiotepa and dexamethasone. Patients who responded received consolidation HDT with carmustine, thiotepa etoposide and transplantation of autologous blood stem cells. Using this approach, the 2-year treatment failure rate was 49 ± 19% and the 2-year overall survival (OS) rate was 63 ± 19%. A further study reported by Doorduyn et al. in 2012 [46] is of particular interest because it was the first to report on the addition of rituximab to the cytotoxic agents. The role of rituximab in the treatment of primary CNS lymphoma is supported by a recently published international randomised trial which showed a significant improvement in response and survival rates with the addition of this monoclonal antibody (mAb) [48]. The most recent and largest phase II trial focusing on the treatment of patients with SCNSL was reported by Ferreri and colleagues [49]. In this trial, 38 patients with SCNSL were treated with a sequential combination of MTX-Ara-C-rituximab plus i.t. liposomal Ara-C followed by HD sequential chemotherapy with cyclophosphamide, Ara-C and VP-16, consolidated with carmustine-thiotepa-conditioned autologous stem cell transplantation (ASCT). Treatment was feasible, with a complete response (CR) rate of 63% and two-thirds of patients who received ASCT in CR were alive at 5 years. This represents clinically relevant therapeutic progress since none of the long-term survivors required whole-brain RT to achieve tumour remission. Moreover, the results of this trial advanced the field beyond previous studies, demonstrating that subgroups of patients older than 65 years with poor PS or concomitant extra-CNS recurrence have the same OS probability as younger and fit patients and those with isolated CNS relapse.

A number of newer agents such as lenalidomide [50], ibrutinib [51] and immune checkpoint inhibitors (CPIs) [52] have shown activity in relapsed or refractory primary CNS lymphoma, but the role of these agents alone and in combination with chemotherapy in the prophylaxis and treatment of early CNS relapse is currently unknown.

Recommendation 1.1: IPI parameters (age >60 years, high LDH levels, poor PS, advanced disease stage and more than one extranodal site) are risk factors for early CNS relapse following first-line treatment of DLBCL, with a direct relationship between the number of unfavourable features and the CNS risk. The involvement of the testes, kidneys, adrenals, breast, bone marrow and bone has also been reported to increase the risk of CNS disease.

Level of evidence: II
Strength of recommendation: B
Consensus: 100% yes (18 voters)

Recommendation 1.2: Patients with DLBCL considered as high risk for CNS relapse should be assessed by brain magnetic resonance imaging (MRI) and CSF assessment by conventional cytology examination and flow cytometry.

Level of evidence: III
Strength of recommendation: C
Consensus: 100% yes (18 voters)

Recommendation 1.3: There is little or no role for i.t. chemotherapy for patients with DLBCL considered as high risk for CNS relapse. i.v. prophylaxis is an option for high-risk patients without evidence of CNS involvement, even though the level of supporting evidence is low. Patients with MRI or CSF evidence of CNS involvement at presentation should receive a combination of anti-lymphoma drugs with good CNS bioavailability, aimed at controlling both CNS and systemic disease, preferably within a clinical trial.

Level of evidence: III
Strength of recommendation: C
Consensus: 100% yes (18 voters)

2. Management of primary resistant HL

The majority of HL patients can be cured with risk-adapted treatment, including chemotherapy and RT [53]. Even when initially diagnosed with advanced-stage disease, 70% of these patients achieve long-term remission [54]. However, depending on initial risk factors and treatment, 10%–30% experience tumour progression or relapse. Of these patients, around 50% can be cured, providing that they are candidates for HDT and ASCT [55, 56]. The median OS after ASCT failure is 2 years [57, 58]. A significantly poorer outcome is observed for patients with primary progressive HL or relapse within the first 12 months after initial therapy [59, 60]. HDT is considered the best available option for patients with primary refractory HL [61–64].

Diagnosis and staging of patients with primary refractory HL. Primary refractory HL is defined either by progression at any time during first-line chemotherapy or RT, or by early relapse up to 3 months after the end of treatment. It is generally recommended to confirm treatment failure and lymphoma subtype at the time of disease progression, but in cases where biopsy is not possible, persisting abnormalities on PET-CT scan with a Deauville score (DS) of 5 during or after therapy should be considered as suspicious of primary refractory disease [65]. Given the risk of false positive PET results, subsequent anti-lymphoma treatment should not be offered based on PET-CT results alone. In the absence of a positive biopsy and/or very clear clinical symptoms of progressive disease, patients should be monitored by repeat scans to confirm the presence of persistent disease, and even in case of persistent or progressive abnormalities, a biopsy is warranted.

Second- and third-line salvage regimens. A number of available salvage chemotherapy regimens are available for the treatment of relapsed HL [66]. The majority of these are platinum-based or gemcitabine-based combinations and no prospective clinical trials indicate any clear benefit (efficacy or toxicity) of one regimen over another one [III, B]. The German Hodgkin Study Group conducted a large, randomised trial which showed no benefit

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from intensification of a platinum-based salvage regimen before HDT [55]. Overall, it is recommended that 2–3 cycles of a salvage regimen are given before evaluating disease response and continuing with HDT and ASCT.

For patients who fail HDT, or who are not candidates for HDT, a range of single-agent chemotherapy regimens have activity. Of cytostatic agents that are non-cross resistant to the conventional first- and second-line regimens, probably the most active is bendamustine, with single-agent response rates of approximately 50% but very limited durability of those responses [67].

Several targeted agents, including mAbs, histone deacetylase inhibitors, phosphoinositide 3-kinase/Akt/mammalian target of rapamycin inhibitors, lenalidomide and proteasome inhibitors, have been investigated in HL. However, by far the most important advances in the targeted treatment of relapsed or refractory HL have been the introduction of brentuximab vedotin (BV) and the immune-CPIs. BV, an antibody-drug conjugate composed of an anti-CD30 antibody conjugated to the microtubule-disrupting agent monomethyl auristatin E, demonstrated high overall and CR rates in patients with relapsed/refractory HL after ASCT [68]. BV received both Food and Drug Administration (FDA) and European Medicines Agency (EMA) approval in 2011 and 2012, respectively, for patients who relapse or progress after ASCT, and for those who are not candidates for ASCT and who do not respond to $\geq$2 lines of chemotherapy. And in 2015 and 2016, the FDA and EMA approved the use of BV for post-transplant consolidation treatment of patients with HL at high risk of relapse or progression. Given its activity, BV could replace a conventional chemotherapy regimen early in the strategy of salvage therapy [III, B], but this possibility requires further evaluation. Preliminary studies of BV given in addition to conventional salvage regimens appear promising [69–72].

More recently, the CPIs nivolumab and pembrolizumab, which are mAbs targeting the programmed cell death protein 1 (PD-1), have demonstrated high activity and durable responses in the majority of patients with relapsed/refractory HL, including chemorefractory patients and those who have failed BV treatment [73, 74].

Unlike conventional chemotherapy, and probably due to the completely novel mechanisms of action, both BV and CPIs lead to response durations which are apparently unrelated to the duration of response to prior chemotherapy treatment lines. This brings particular hope for patients with primary refractory disease, since so far this group has had a much lower likelihood of benefit from treatment than patients with longer duration of remission.

The optimal sequence of BV and CPIs is currently not clear, but ongoing studies are directly comparing BV and CPIs. Even though they are only approved for use as single agents, the combination of CPIs with BV has demonstrated impressive activity as well as favourable toxicity in preliminary studies [75, 76].

Evaluation of disease response before HDT and ASCT. Screening for response to salvage treatment is fundamental to patient care and should be carried out with PET-CT. Based on PET-guided evaluation, every effort should be made to increase the proportion of chemosensitive patients and to eventually achieve complete metabolic remission using combinations of non-cross-resistant chemotherapy and/or novel drugs [71].

ASCT for primary refractory HL. According to retrospective and prospective as well as randomised studies, HDT followed by ASCT can rescue 30%–80% of relapsed/refractory classical HL patients. Refractoriness to first-line chemotherapy is the strongest factor predicting a poor outcome after ASCT. Patients in this category were not included in randomised trials, and autografting resulted in durable progression-free survival (PFS) in 30%–40% – once again supporting the general concept of poorer outcome in chemorefractory patients compared with chemosensitive patients [IV, B].

Several reports indicate that a dose-increased strategy, including double transplantation, is a valuable option in patients with high-risk relapsing/refractory HL, taking into account that definitions of high-risk status vary between studies. In 2008, the Groupe d'Etude des Lymphomes de l'Adulte (GELA) and the Société Française de Greffe de Moelle (SFGM) proposed a risk-adapted strategy in relapsed HL based on the separation of patients into three prognostic groups [77]. Tandem ASCT results suggested a benefit for high-risk patients compared with previous reports of outcomes with single ASCT. Some patients achieved partial or complete remission with their second transplant, and overall outcomes for patients experiencing partial, complete or uncertain complete remission (defined by CT alone) did not differ significantly if the patients had received double transplantation [III, B] [77]. This approach has also been tested by other investigators with similar conclusions [78, 79].

Consolidation therapy after ASCT. The prospective, randomised, placebo-controlled AETHERA trial demonstrated that early consolidation with BV after ASCT improves PFS in patients with HL at high risk of relapse or progression after ASCT [80]. More than 50% of the patients in both groups in AETHERA were primary refractory HL patients [I, B]. The most recent update of this study showed a hazard ratio of 0.58 (i.e. a 42% reduction in the risk of a PFS event). Median PFS was not reached in the BV arm versus 15.8 months in the placebo arm. Three-year PFS was 61% in the BV arm versus 43% in the placebo arm. Three years after randomisation of the last patient, PFS curves for both the BV and placebo arms had reached plateaus, indicating that the effect of BV consolidation is a lasting one and that this treatment may have the potential to eradicate viable residual disease. No difference in OS was observed, perhaps in part reflective of the fact that patients in the placebo arm who progressed were offered treatment in a different BV trial [81].

Allogeneic stem cell transplantation (alloSCT) for refractory HL. The prognosis of patients who fail ASCT is poor. A joint European Group for Blood and Marrow Transplantation (EBMT) and Gruppo Italiano per il Trapianto di Midollo Osseo (GITMO) retrospective analysis of 462 patients who relapsed or progressed after ASCT showed a median time from ASCT to relapse of 7 months (range of 1–78 months) and a 5-year OS for the entire cohort of just 32% [82]. Clinical results from retrospective trials of alloSCT reported in the early nineties were disappointing, likely due to the inclusion of heavily pretreated patients who had received extended RT and were allografted in the presence of active disease after myeloablative conditioning with bone marrow stem cells. However, in the late nineties, the SCT scenario changed substantially with the introduction of reduced intensity conditioning regimens. In fact, several retrospective and

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prospective phase II clinical trials reported clinically significant reductions in non-relapse mortality to below 30%, resulting in a renewed interest in alloSCT. On average, PFS ranged from 20% to 42% and OS from 25% to 57% [IV, C] [82–86]. The EBMT considers alloSCT as a valid treatment alternative for patients with relapsed HL after ASCT if they have chemosensitive disease and an appropriate stem cell donor [87].

The current availability of active drugs, including BV [68], PD-1 inhibitors [88] and bendamustine [89], has enabled substantially high rates of objective responses in patients who previously failed ASCT, thus resulting in significant improvements in the quality and quantity of clinical responses achieved by patients who become eligible for alloSCT after failed autografting. Interestingly, these treatments share a favourable toxicity profile, thus allowing patients to achieve a good PS at the time of allografting.

AlloSCT could also be a viable option for patients with an incomplete response to salvage chemotherapy, particularly because better results are obtained when this treatment is applied earlier [IV, C] [90]. With conventional agents for induction of remission, the survival of these patients is poor, and most of them die due to disease progression. The availability of novel agents that result in objective responses may eventually mean increased eligibility for alloSCT. On the other hand, long-term follow-up results from the phase II study of BV in relapsed/refractory HL show that among patients reaching a complete remission as best response, 38% were still alive and progression-free at a minimum of 5 years after the last dose of BV. This suggests that BV monotherapy may have curative potential in a subset of patients with relapse post-HDT, even without subsequent alloSCT, which until recently was regarded as the only curative option for HL patients failing HDT [91].

The combination of CPIs and alloSCT is an area of concern, since increased rates of severe graft-versus-host disease (GvHD) have been observed in patients treated with CPIs following alloSCT. However, the increased toxicity may be outweighed by improved efficacy leading to durable remissions [92, 93]. Other studies have shown that remissions induced by CPIs and consolidated with alloSCT can be durable in many cases [94]. In order to reduce the risk of GvHD, it is generally recommended to hold CPI treatment a few months before the alloSCT, but this advice is based on biological rationale rather than clinical evidence [94].

RT for relapsed or refractory HL. RT is tolerable in most patients with relapsed or refractory HL, including those with primary resistant disease. Even patients with primary resistant disease have a good chance of response to RT [95]. In a study of 56 patients who received salvage RT for relapse post-ASCT, 65% had durable local disease control after 2 years [96]. RT should be considered for patients with primary resistant HL, both as part of induction or as consolidation in patients with localised or bulky disease, and as part of standard palliative treatment of incurable HL.

Recommendation 2.1: For patients with primary resistant HL, there is no evidence to suggest a benefit from treating any differently to other patients with relapsed HL. As such, these patients should be treated the same as other patients with relapsing HL, preferably as part of a clinical trial.

Level of evidence: III
Strength of recommendation: D
Consensus: 100% yes (18 voters)

Recommendation 2.2: The use of BV and CPIs seem to be particularly beneficial for patients with primary resistant HL who are less likely to benefit from conventional therapies. Consolidation with BV after HDT and ASCT is recommended for patients with primary resistant HL.

Level of evidence: II
Strength of recommendation: B
Consensus: No vote obtained

Recommendation 2.3: AlloSCT has a limited role for patients with primary resistant HL but can be considered in selected patients with a good, durable remission and a suitable donor.

Level of evidence: IV
Strength of recommendation: D
Consensus: 100% yes (18 voters)

3. Management of PBL

PBL is a rare and distinct entity classified by the World Health Organization as an aggressive subtype of DLBCL with immunoblastic and/or plasmablastic morphology, high proliferation rate and immunophenotypic evidence of terminal B-cell differentiation. The immunophenotype is positive for CD79a, MUM-1, BLIMP-1, CD38 and CD138, but negative for the B-cell markers CD19, CD20 and PAX-5. MIB-1 is positive in most or all neoplastic cells. About 70%–80% of cases express Epstein–Barr virus-encoded RNA (EBER). Among the most frequently detected genomic changes are chromosomal translocations involving the *MYC* gene, usually in association with the immunoglobulin heavy chain, which are detected in half of cases. However, whether *MYC* translocations represent initiating or late genetic events in PBL pathogenesis is unknown. Gene expression profiling in PBL has shown that it has a transcriptional profile distinct from DLBCL, with differences in activation of B-cell receptor signalling and targets of the transcription factors *MYC* and *MYB* [97].

Recommendation 3.1: For human immunodeficiency virus (HIV)-negative patients with suspected PBL, diagnostic assessment should include an immunohistochemistry panel of CD38, CD20, PAX5, CD138, EBER, CD30, MUM-1, Kappa-lambda, HHV8 and ALK

Level of evidence: IV
Strength of recommendation: C
Consensus: 100% yes (18 voters)

PBL is strongly associated with HIV infection and can also arise in other patients with immunodeficiency states (e.g. organ transplant recipients, the elderly), but is also seen in immunocompetent individuals. The incidence of HIV-associated PBL accounts for approximately 2% of all acquired immunodeficiency syndrome-related lymphomas. For immunocompetent patients, the incidence is approximately 0.3% of all non-HL [98]. In a review of 590 patients with PBL [99], 63% were HIV-positive PBL, 28% were HIV-negative PBL, 6% were post-transplant PBL and 3% were transformed PBL. HIV-negative PBL affects female patients in 34% of cases, and the median age at presentation is 55 years. Oral involvement is common (40%), although PBL has a more heterogeneous pattern in terms of sites of involvement in immunocompetent individuals [100]. Advanced clinical stage,

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B symptoms and bone marrow involvement are present in 25% of HIV-negative patients with PBL.

The prognosis of patients with PBL is poor. A systematic review of 76 patients with HIV-negative PBL showed a median OS of only 9 months and a 2-year OS rate of 10% [99]. The prognostic value of IPI factors in PBL relies primarily on advanced disease stage and poor PS as indicators of a worse outcome, since age, LDH levels and bone marrow involvement do not appear to affect outcomes in HIV-positive patients [101].

There is no standard of care for patients with PBL. In particular, the use of CHOP is considered inadequate, and some guidelines recommend more intensive regimens such as EPOCH (etoposide/prednisone/vincristine/cyclophosphamide/hydroxydaunomycin), CODOX-M (cyclophosphamide/vincristine/doxorubicin/methotrexate)/IVAC (etoposide/ifosfamide/cytarabine) or hyper-CVAD (cyclophosphamide/vincristine/doxorubicin/dexamethasone) [102]. However, several studies of PBL treated with chemotherapy regimens more intensive than CHOP have failed to show a survival benefit [101, 103]. Therefore, PBL should be treated as high-risk DLBCL, but due to the lack of CD20 positivity, treatment with anti-CD20 mAbs is not indicated.

Only few cases of PBL have reported the use of prophylaxis to minimise the risk of CNS involvement. Moreover, there is currently no evidence that the use of CNS prophylaxis should be any different in PBL compared with other high-risk subtypes of DLBCL.

RT has been used as part of treatment in some PBL cases, but no conclusion can be made from this limited experience, and therefore RT is recommended only in the palliative setting [100].

The proteasome inhibitor bortezomib, alone and in combination with chemotherapy, has been used with some degree of efficacy in HIV-negative patients with relapsed PBL. In a recent series of three previously untreated patients with PBL (one of whom was HIV-negative), durable responses were achieved with bortezomib combined with dose-adjusted EPOCH [104]. In another report, three HIV-positive patients with PBL demonstrated durable remissions following treatment with bortezomib (V)-CHOP, suggesting that this regimen may provide improved efficacy as initial therapy for PBL [105]. However, these encouraging results are based on anecdotal cases and further cumulative experience is needed.

Recommendation 3.2: HIV-negative patients with PBL should be treated the same as other high-risk subtypes of DLBCL, although rituximab should not be used.

Level of evidence: IV
Strength of recommendation: C
Consensus: 100% yes (18 voters)

Recommendation 3.3: Although bortezomib can be safely combined with CHOP, this has not led to improved outcomes and further studies are required.

Level of evidence: V
Strength of recommendation: C
Consensus: 100% yes (18 voters)

The role of SCT in patients with PBL has been assessed and it appears that chemotherapy-sensitive PBL patients might benefit from ASCT in first remission. A case series of nine HIV-negative patients with PBL (who responded to chemotherapy) reported encouraging results, with a 5-year OS rate of 60% [106]. The experience with HDT followed by ASCT in the relapsed setting is rather limited. The role of alloSCT is unknown and can only be recommended as a part of a clinical trial.

Recommendation 3.4: HDT-ASCT may play a role in the management of PBL but further studies are required, since available data are from casuistic reports of selected patients.

Level of evidence: IV
Strength of recommendation: D
Consensus: 100% yes (18 voters)

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Appendix

ESMO Lymphoma Consensus Conference Panel Members

Christian Buske, Comprehensive Cancer Center Ulm and Department of Internal Medicine III, Institute of Experimental Cancer Research, University Hospital, Ulm, Germany; Martin Dreyling, Medizinische Klinik III, Klinikum der Universität München/LMU, Munich, Germany; Andrés J.M. Ferreri, Unit of Lymphoid Malignanciegy, IRCCS San Raffaele Scientific Institute, Milan, Italy; Paul Fields, Department of Haematology, Guys and St Thomas' and King's College Hospitals, London, United Kingdom; Gianluca Gaidano, Division of Hematology, Department of Translational Medicine, Amedeo Avogadro University of Eastern Piedmont, Novara, Italy; Valentin Goede, Department of Internal Medicine, University Hospital Cologne, Germany; Martin Hutchings, Department of Haematology, Rigshospitalet, Copenhagen, Denmark; Marco Ladetto, Hematology Division, Azienda Ospedaliera Santi Antonio e Biagio e Cesare Arrigo, Alessandria, Italy; Steven Le Gouill, Centre Hospitalo-Universitaire de Nantes, UMR892 team 10, CIC Nantes, France; Stefano Luminari, Hematology, Arcispedale S. Maria Nuova, IRCCS Reggio Emilia, and Department of Diagnostic, Clinical and Public Health Medicine, University of Modena and Reggio Emilia, Modena, Italy; Ulrich Mey, Department of Oncology and Haematology, Kantonsspital Graubünden, Chur, Switzerland; Peter de Nully Brown, Department of Haematology, Rigshospitalet, Copenhagen, Denmark; Michael Pfreundschuh, Innere Medizin I, University Klinik des Saarlandes, Hamburg, Germany; Christiane Pott, Second Medical Department, University Hospital Schleswig-Holstein, Kiel, Germany; Norbert Schmitz, Department of Hematology, Oncology and Stem Cell Transplantation, Asklepios Klinik St. Georg, Hamburg, Germany; Pierre Soubeyran, Department of Medical Oncology, Institut Bergonié, Comprehensive Cancer Centre, Bordeaux, France; Michele Spina, Division of Medical Oncology A, National Cancer Institute, Aviano, Italy; Reinhard Stauder, Haematology and Oncology Department, Innsbruck Medical University, Innsbruck, Austria; Anna Sureda Balari, Servei d'Hematologia, Institut Català d'Oncologia – Hospital Duran i Reynals, Barcelona, Spain; Marek Trněný, Institute of Hematology and Blood Transfusion, Ist Dept Medicine, 1st Fac Medicine, Charles University, General Hospital, Prague, Czech Republic; Gustaaf van Imhoff, Section of Hematology, University of Groningen, Groningen, The Netherlands; Jan Walewski, Department of Lymphoid Malignancies, Maria Sklodowska-Curie Memorial Cancer Centre and Institute of Oncology, Warsaw, Poland; Ulrich Wedding, Department of Palliative Care, University Hospital, Jena, Germany; Alberto Zamò, Department of Diagnostics and Public Health, University of Verona, Verona, Italy; Emanuele Zucca, Lymphoma Unit, Oncology Institute of Southern Switzerland, Ospedale San Giovanni, Bellinzona, Switzerland.

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